Janssen Products, LP
800 Ridgeview Drive
Horsham, PA 19044
www.janssenbiotech.com

**Important Update Regarding the Availability of DOXIL® (doxorubicin HCl liposome injection)**

August 5, 2011

Dear Healthcare Provider:

As a follow-up to our ongoing updates about the current supply shortage of DOXIL® in the U.S. market, we are pleased to provide an update about a new physician allocation process to obtain DOXIL® supply as it becomes available.

As of today, a modest supply of DOXIL® is now available. To allow patients currently on DOXIL® the option to continue their current course of therapy, we have set up a physician allocation process called the DOXIL® C.A.R.E.S. Physician Access Program. Please be advised that this is a limited supply of DOXIL® and we encourage you to enroll your current patients on DOXIL® immediately.

For additional details about the DOXIL® C.A.R.E.S. Physician Access Program, including how to enroll your patients currently on DOXIL®, please visit www.DOXIL.com. The site includes additional program information, enrollment forms, and the most current updates on the supply situation.

As DOXIL® supply will remain intermittently available in the coming months, first priority will be given to patients currently on DOXIL®. We continue to recommend that you do not start any new patients on DOXIL® until adequate supply becomes available.

We understand the impact this situation may cause with patients currently on DOXIL®. As an additional resource, please refer to national treatment guidelines, such as those of the National Comprehensive Cancer Network® (NCCN). Although there are no generic alternatives to DOXIL® available in the US, and conventional doxorubicin is not bioequivalent to DOXIL®, treatment decisions can be individualized after discussing options with your patients. As a reminder, you cannot substitute DOXIL® on milligram-per-milligram basis with doxorubicin HCl.

Please see Important Safety Information, including Boxed Warnings on the next page and accompanying full Prescribing Information.

DOXIL® continues to be a cornerstone of our product offering for the healthcare community, and we are deeply committed to improving the availability of DOXIL® for patients and physicians as soon as possible. If you have any clinical questions about DOXIL®, please contact our Medical Information Department at 800-526-7736 (800-JANSSEN).

Sincerely,

Peter Callegari, MD
Vice President, Medical Affairs
Janssen Products, LP

 8/11 08D11031R

# *IMPORTANT SAFETY INFORMATION*

## *BOXED WARNINGS*

**Cardiotoxicity, infusion reaction, myelosuppression, liver impairment, substitution**

- **The use of DOXIL® may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m²**
  - **Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dose**
  - **Cardiac toxicity may also occur at lower cumulative doses (400 mg/m²) in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy**
- **Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL®. In most patients, these reactions have resolved within several hours to a day once the infusion is terminated. In some patients, reactions resolved with slowing of the infusion rate**
  - **Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have occurred. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use**
  - **The initial rate of infusion should be 1 mg/min to minimize the risk of infusion reactions**
- **Severe myelosuppression may occur**
- **DOXIL® dosage should be reduced in patients with impaired hepatic function**
- **Accidental substitution has resulted in severe side effects. Do not substitute for doxorubicin HCl on a mg per mg basis**

## *CONTRAINDICATIONS*

- Patients with a history of hypersensitivity reactions to a conventional doxorubicin formulation or the components of DOXIL®
- Nursing mothers

## *ADDITIONAL SAFETY INFORMATION*

- Cardiac function should be carefully monitored
  - Congestive heart failure or cardiomyopathy may occur after discontinuation of anthracycline therapy
  - For patients with a history of cardiovascular disease, or if the results of cardiac monitoring indicate possible cardiac injury, the benefit of therapy must be weighed against the risk of myocardial injury
  - In the randomized multiple myeloma study, 25 patients (8%) in the VELCADE® arm and 42 patients (13%) in the DOXIL® plus VELCADE® arm experienced left ventricular ejection fraction decrease (defined as absolute decrease ≥15% over baseline or a ≥5% decrease below institutional lower limit of normal)
- Myelosuppression may occur; frequently monitor complete blood count (including platelet count), at least prior to each dose of DOXIL®
  - In patients with recurrent ovarian cancer, hematologic toxicity (based on platelet count or absolute neutrophil count) may require dose reduction or delay in administration of DOXIL®
  - In patients with multiple myeloma, hematologic toxicity (based on platelet count, absolute neutrophil count, hemoglobin level, or neutropenia with fever) may require dose reduction, delay in administration, or suspension of DOXIL® and/or VELCADE®
  - Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage
  - Sepsis occurring during neutropenia has resulted in discontinuation of treatment and in rare cases of death
- DOXIL® may potentiate the toxicity of other anticancer therapies, especially hematologic toxicities, when used in combination with other therapies that suppress bone marrow
- Hand-foot syndrome (HFS) may occur during therapy with DOXIL®
  - Based on HFS toxicity grade, dose reduction, delay in administration, or discontinuation of DOXIL® may be required
  - HFS was generally observed after 2 to 3 cycles of treatment, but may occur earlier
    - The reaction was mild in most patients, resolving in 1 to 2 weeks
    - The reaction can be severe and debilitating in some patients, resulting in discontinuation of therapy
- DOXIL® is an irritant, not a vesicant; use precautions to avoid extravasation
- DOXIL® can cause fetal harm when used during pregnancy
- Recall reaction has occurred with DOXIL® administration after radiotherapy
- DOXIL® may interact with drugs known to interact with the conventional formulation of doxorubicin HCl
- In patients with recurrent ovarian cancer, the most common all-grade adverse reactions (ARs) ≥20% (DOXIL® vs topotecan, respectively) included: asthenia (40% vs 51%), fever (21% vs 31%), nausea (46% vs 63%), stomatitis (41% vs 15%), vomiting (33% vs 44%), diarrhea (21% vs 35%), anorexia (20% vs 22%), dyspnea (15% vs 23%), HFS (51% vs 1%), and rash (29% vs 12%)
  - In addition, 19% vs 52.3% reported alopecia (all grades)
  - Grade 3/4 hematologic ARs reported in ≥5% (DOXIL® vs topotecan, respectively) were neutropenia (12% vs 76%) and anemia (6% vs 29%)
- In patients with multiple myeloma, the most common all-grade adverse reactions ≥20% (DOXIL® plus VELCADE® vs VELCADE®, respectively) included: neutropenia (36% vs 22%), thrombocytopenia (33% vs 28%), anemia (25% vs 21%), fatigue (36% vs 28%) , pyrexia (31% vs 22%), asthenia (22% vs 18%), nausea (48% vs 40%), diarrhea (46% vs 39%), vomiting (32% vs 22%), constipation (31% vs 31%), mucositis/stomatitis (20% vs 5%), peripheral neuropathy (42% vs 45%), neuralgia (17% vs 20%), and rash (22% vs 18%)
  - In addition, 19% vs <1% reported HFS

**Please see accompanying full Prescribing Information, including Boxed WARNINGS, for DOXIL®.**